Supplementary Information (SI) for Journal of Materials Chemistry B.
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Appendix A. Supplementary data

Bioactive Zeolitic Imidazolate Frameworks Nanoconjugates as Synergistic Drug Delivery Agents for Cancer Nanotherapeutics

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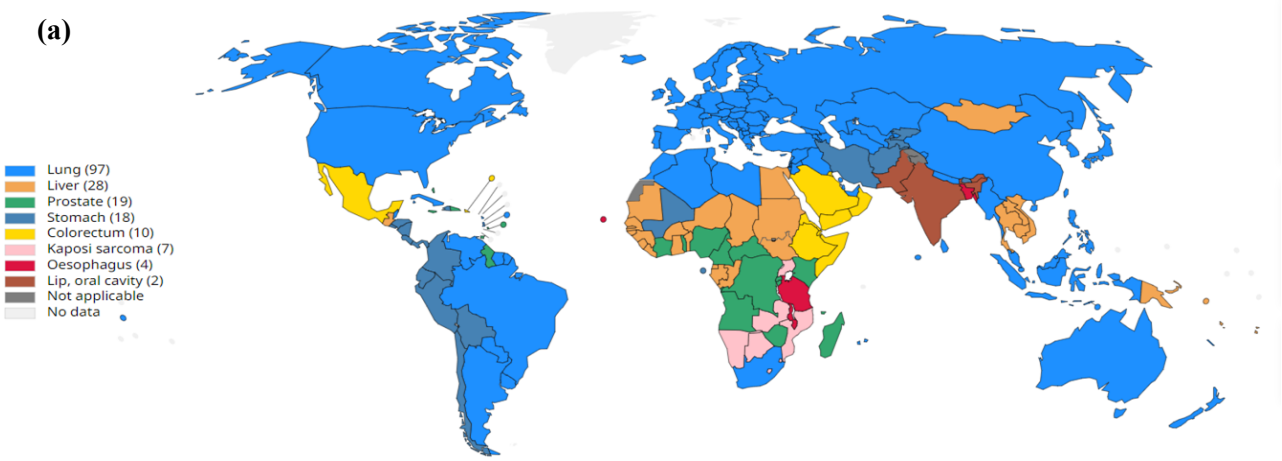
(a)



(b)

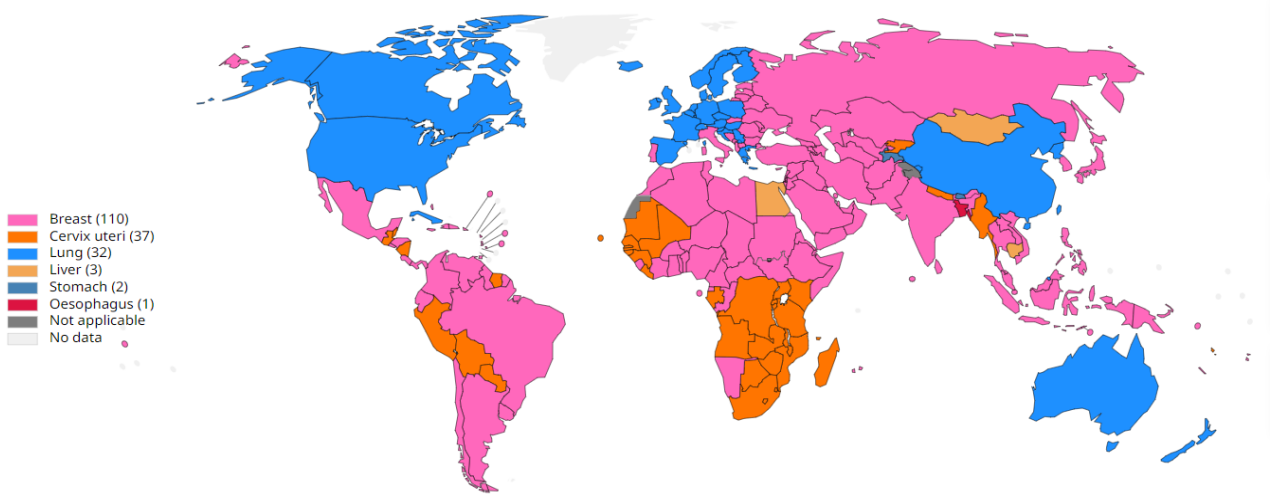


Figure S1. (a) Top cancer per country, the estimated number of deaths in 2020, males, ages 0-74. The data used to prepare the map were taken from GLOBOCAN 2020. (b) Top cancer per country, the estimated number of deaths in 2020, females, ages 0-74. The data used to prepare the map were taken from GLOBOCAN 2020

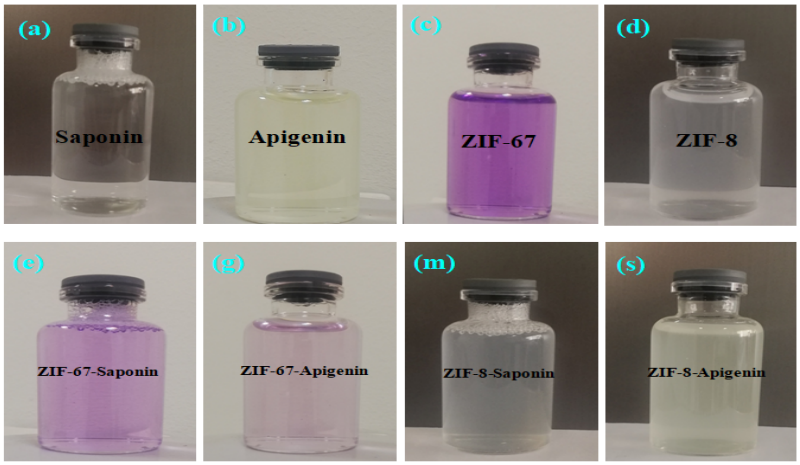
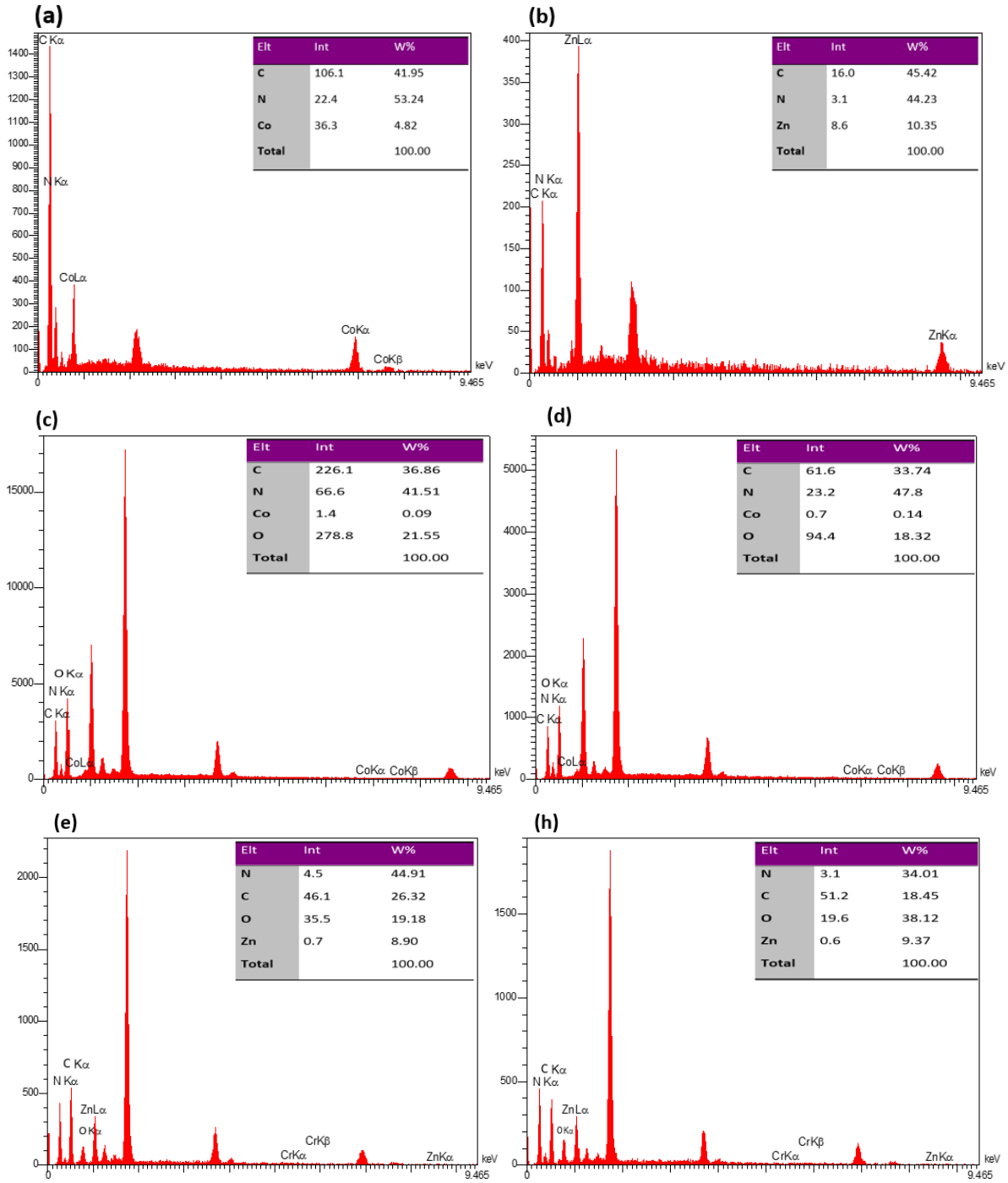


Figure S2. The bottom figures nanoparticles with natural products prepared are shown. (a) saponin. (b) apigenin (c) ZIF-67, (d) ZIF-8, (e) ZIF-67-Saponin, (g) ZIF-67-Apigenin, (m) ZIF-8-Saponin, (s) ZIF-8-Apigenin.

Energy Dispersive X-ray (EDX):



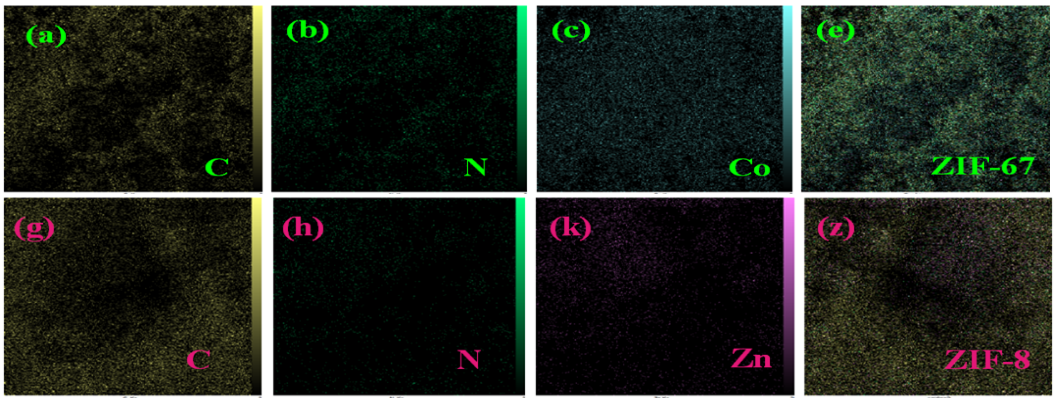


Figure S3. EDX analysis of (a) ZIF-67, (b) ZIF-8, (c) ZIF-67-saponin, (d) ZIF-67-apigenin, (e) ZIF-8-saponin and (h) ZIF-8-apigenin. EDS element mapping of (a,b,c,e) ZIF-67 and (g,h,k,z) ZIF-8.

BET:

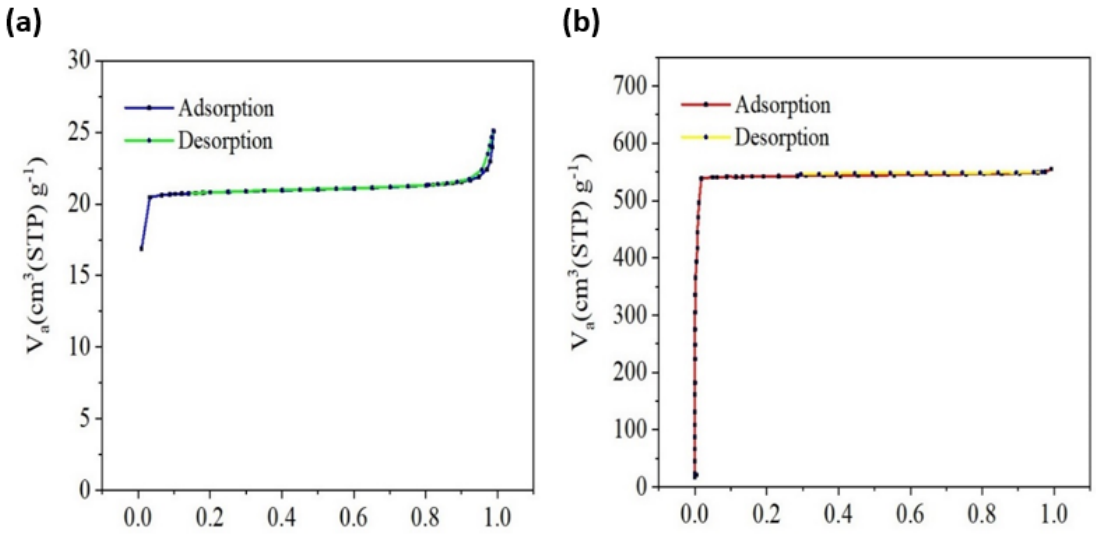


Figure S4. N_2 adsorption–desorption isotherms of ZIF-8 **(a),** and ZIF-67 **(b)** at 77 K

Cellular Uptake Study:

To demonstrate the cell imaging performance, MCF-7 and PDL cells were cultured with kinds of bioactive ZIF-67 and ZIF-8 with saponin and apigenin at a concentration of 1000 μg/mL for different times (zero moment, 4 h and 24 h), and tracked through the fluorescent images of the nanoparticles in cells. images of MCF-7 and PDL cells were obtained and are shown in Figures S5 and S6. Figures (a_1 to l_4) are the images under bright field and fluorescent images after cultured with samples for zero moment, 4 h, and 24 h and

show the treated typical morphology of PDL cells. Analyzing Figures 9 (a_1 to l_4) provides valuable insights into the impact of the samples on the cellular characteristics of PDL cells and aids in understanding their potential role in influencing the behavior or function of these cells.

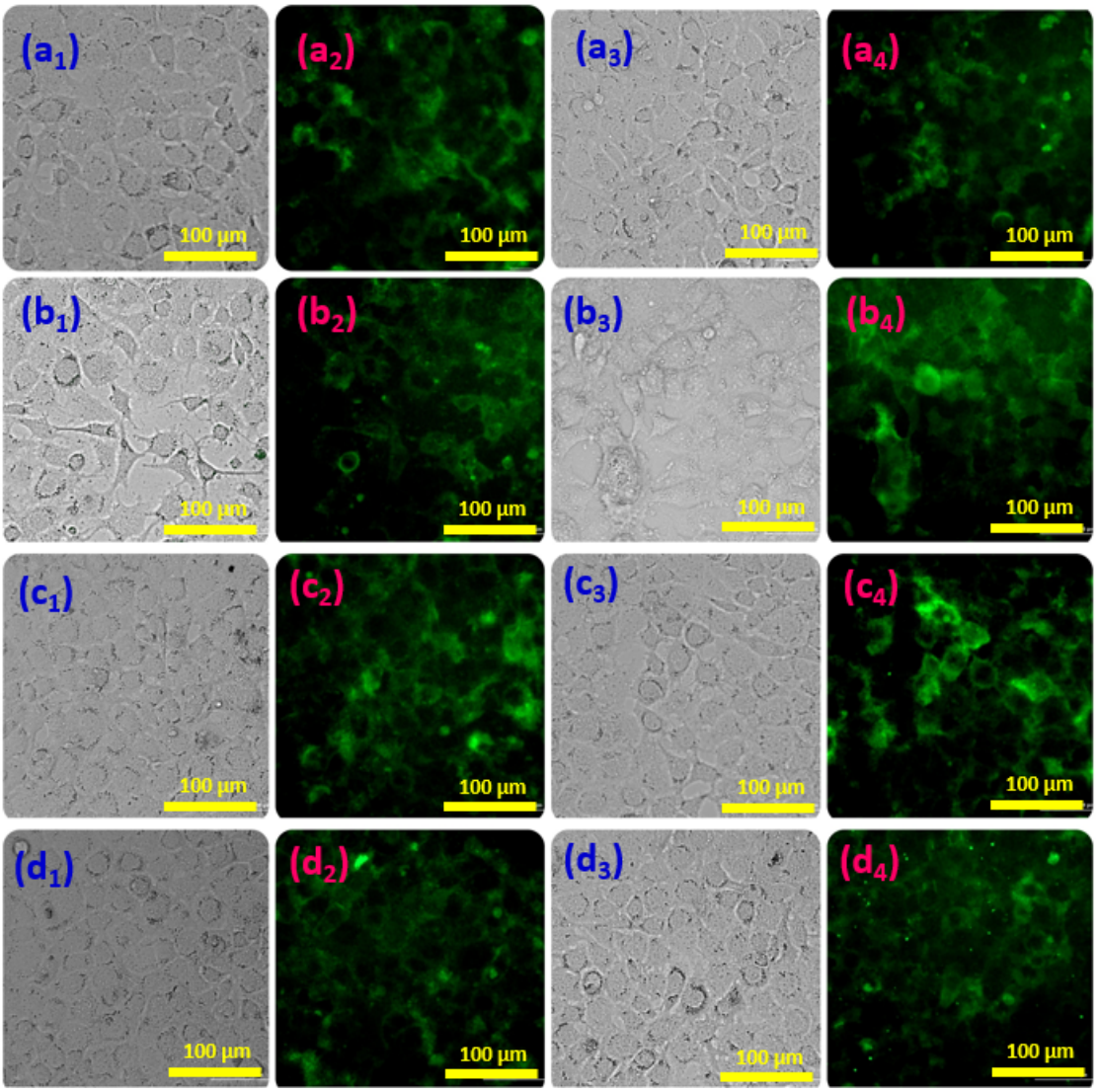
Through the zero moment and 4 h observed time points, the treated PDL cells don't exhibit distinct morphological alterations compared to the control group. But after 24 hours, the morphology of the cells can be seen with a slight change. In the white field and fluorescence images of PDL cells treated with samples (i_1, i_2) bioactive ZIF-67, (i_3, i_4) bioactive ZIF-8 after 24 hours, the healthy morphology of the cells can be seen, while the cells treated with (j_1, j_2) Saponin, and (j_3, j_4) Apigenin compared to the control sample, in addition to the abnormal morphology, they have a lower number of cells, which shows that the natural products of saponin and apigenin are completely toxic to normal cells in a long period.

Figures S6. (m_1 to s_4) are the images under bright field and fluorescent images after cultured with samples for zero moment, 4 h, and 24 h and show the treated typical morphology of MCF-7 cells. Fluorescent images under 325 nm excitation light. Bioactive ZIF-67, ZIF-8, and combined with saponin and apigenin were endocytosed by cells, which made the morphology of the cells clearly shown through fluorescence.

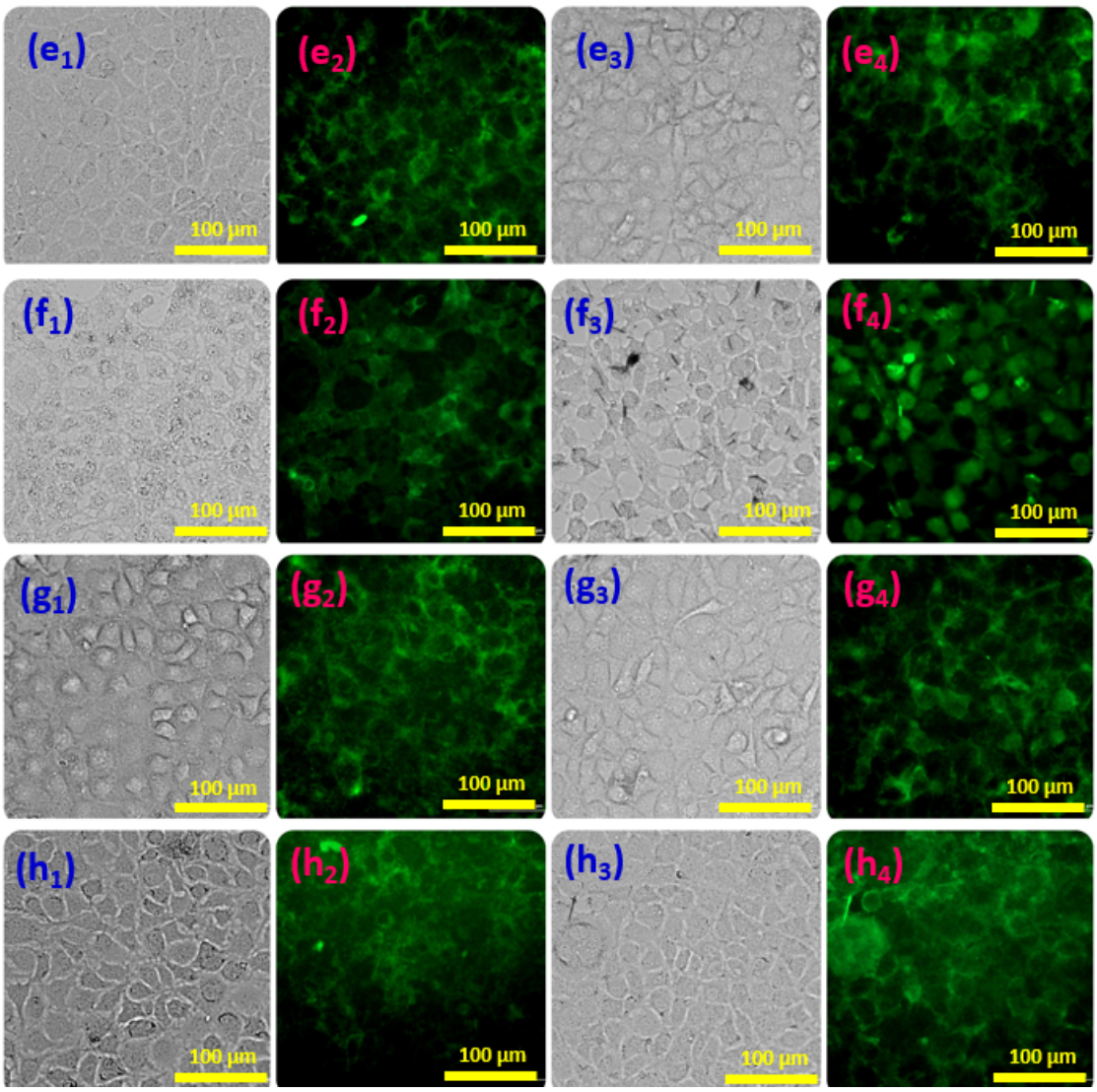
According to the fluorescent photos, it is clear that bioactive ZIF-67 and ZIF-8 samples have high fluorescence, and when they were combined with natural proacts, their fluorescence intensity did not decrease. It is obvious that bioactive ZIF-67, ZIF-8, and combined with saponin and apigenin are only located in the cytoplasm, not in the nucleic.

The lowest fluorescent intensity was related to figures at zero moments (Figures S6 . m_2 to p_4), but as the incubation time increased, the absorption of nanocarriers into the cytoplasm of cells increased and after 4 hours (Figures S6 . q_1 to t_4) and 24 hours (Figures S6 . u_1 to x_4) to the order of fluorescence intensity of the cells also increased. The remarkable thing is that after 24 hours, the intensity of the fluorescence of nanocarriers did not decrease, which shows that bioactive ZIFs have high stability in the cellular environment. Fluorescent images of samples Figures S6. (o_1,o_2) ZIF-67-Saponin, (o_3,o_4) ZIF-67-Apigenin, (p_1,p_2) ZIF-8-Saponin, (p_3,p_4) ZIF-8-Apigenin showed in The zero moment of cellular internalization of the samples is very low. The number of MCF-7 cells has not changed compared to the control sample, and the morphology is also stable. But after 4 hours and 24 hours, the internalization of the samples in the cells increased and the fluorescence of the cells was observed more intensely. In addition, the number of cells decreased and the morphology of MCF-7 cells changed completely.

PDL Intracellular uptake 2D-fluorescence images after Zero moment



PDL Intracellular uptake 2D-fluorescence images after 4 h



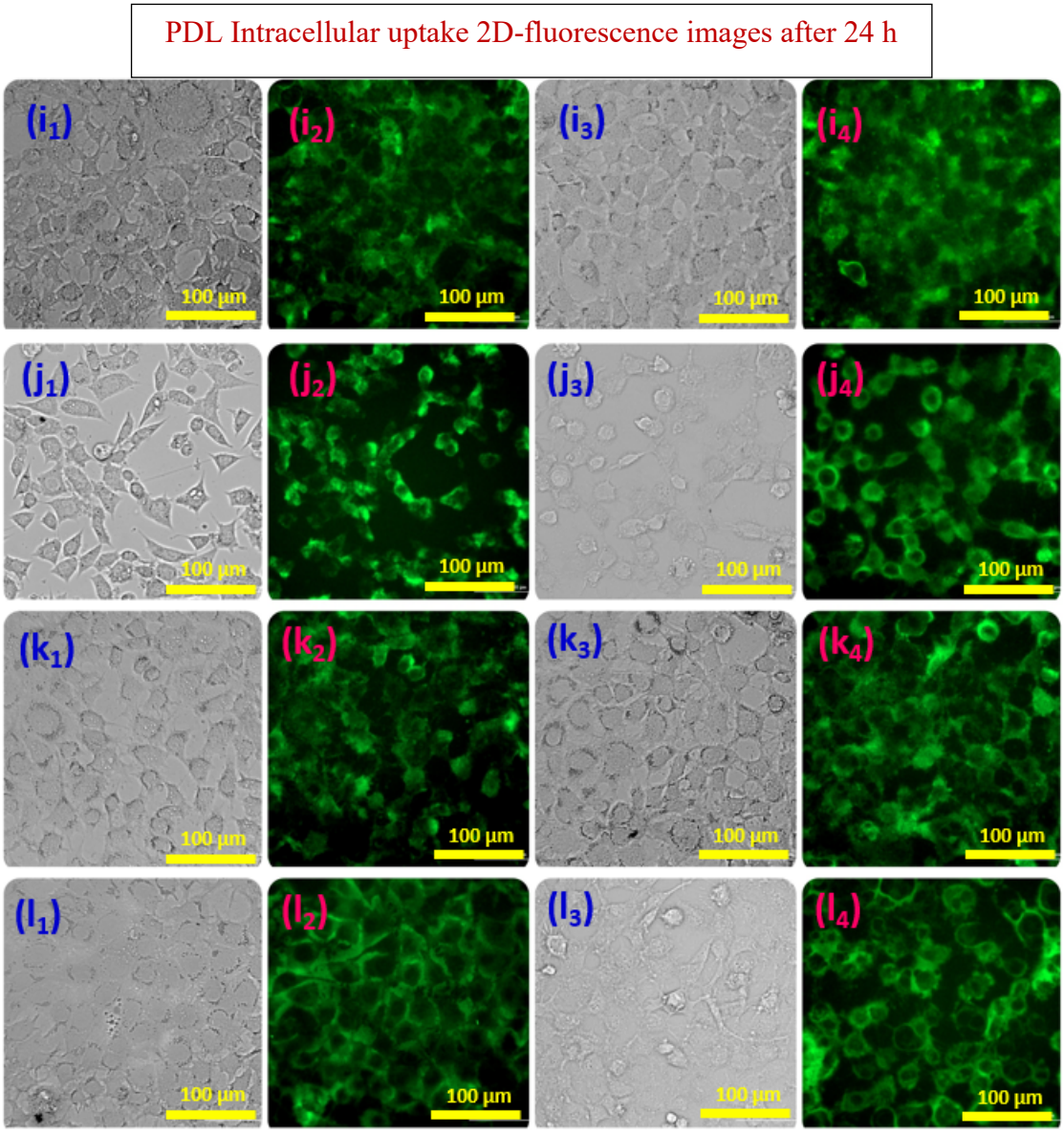


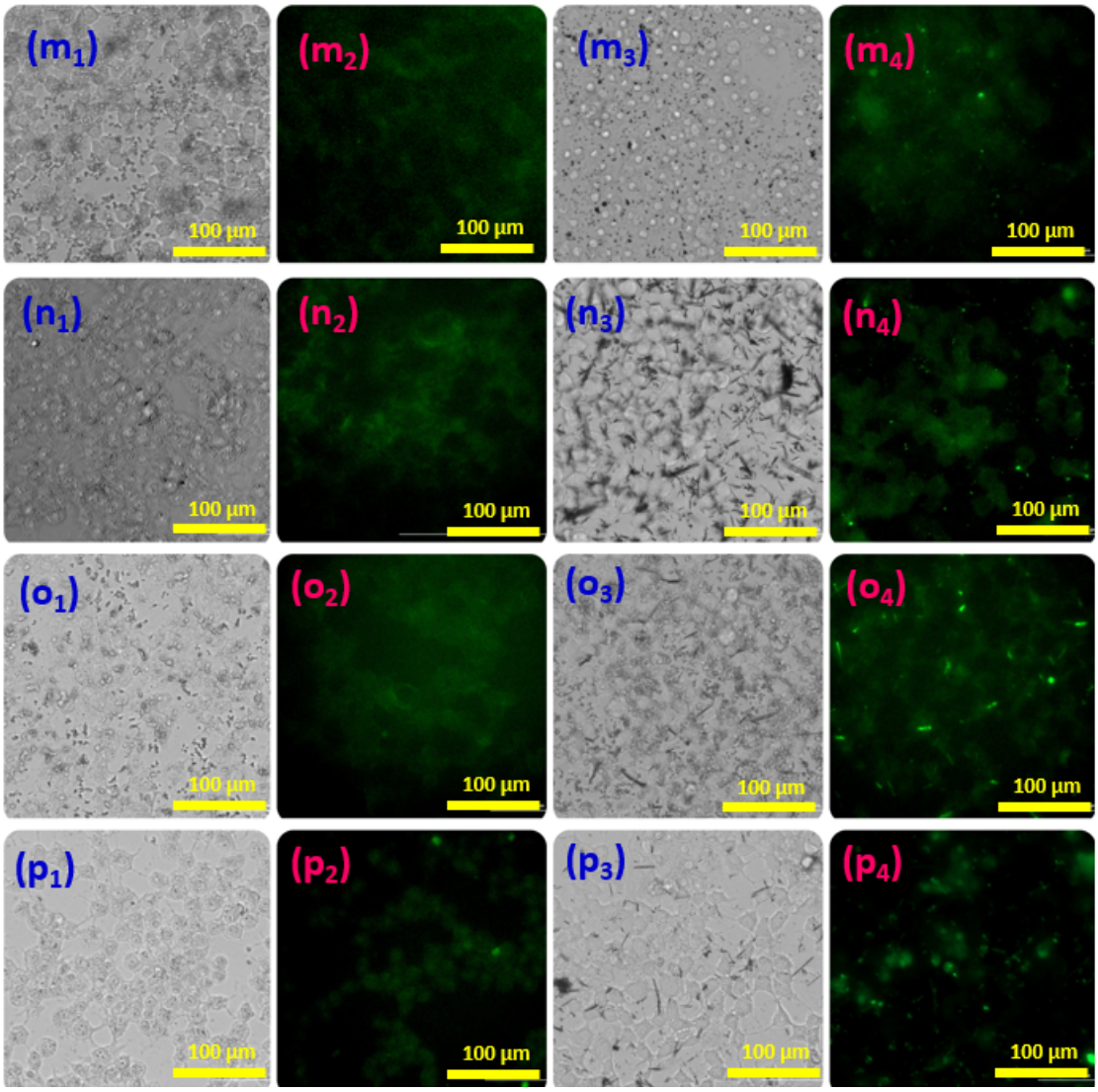
Figure S5. Intracellular uptake 2D-fluorescence images after zero moment, 4 h, and 24 h of treatments at 37° C with 95% humidity. Excitation wavelength, 360 nm. Wavelength ranges, 500–570 nm for green channel.

Intracellular uptake 2D-fluorescence images after zero moment (PDL Cell) :(a_1,a_2)ZIF-67, (a_3,a_4) ZIF-8 , (b_1,b_2) Saponin , (b_3,b_4) Apigenin , (c_1,c_2) ZIF-67-Saponin, (c_3,c_4) ZIF-67-Apigenin , (d_1,d_2) ZIF-8-Saponin , (d_3,d_4) ZIF-8-Apigenin.

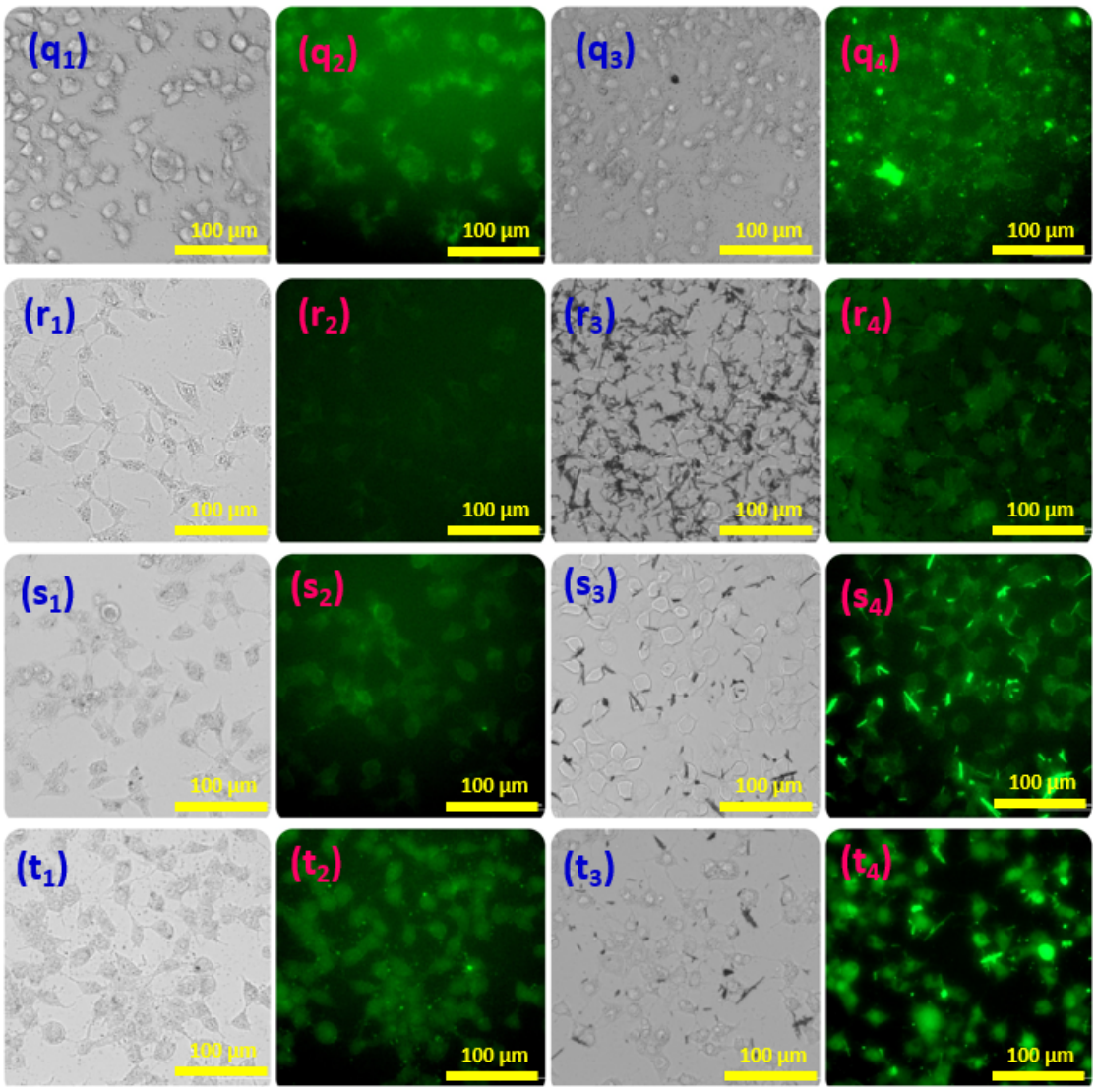
Intracellular uptake 2D-fluorescence images after 4 h (PDL Cell) :(e_1,e_2)ZIF-67, (e_3,e_4) ZIF-8 , (f_1,f_2) Saponin , (f_3,f_4) Apigenin , (g_1,g_2) ZIF-67-Saponin, (g_3,g_4) ZIF-67-Apigenin , (h_1,h_2) ZIF-8-Saponin , (h_3,h_4) ZIF-8-Apigenin .

Intracellular uptake 2D-fluorescence images after 24 h (PDL Cell) :(i_1,i_2)ZIF-67, (i_3,i_4) ZIF-8 , (j_1,j_2) Saponin , (j_3,j_4) Apigenin , (k_1,k_2) ZIF-67-Saponin, (k_3,k_4) ZIF-67-Apigenin , (l_1,l_2) ZIF-8-Saponin , (l_3,l_4) ZIF-8-Apigenin .

MCF-7 Intracellular uptake 2D-fluorescence images after Zero moment



MCF-7 Intracellular uptake 2D-fluorescence images after 4 h



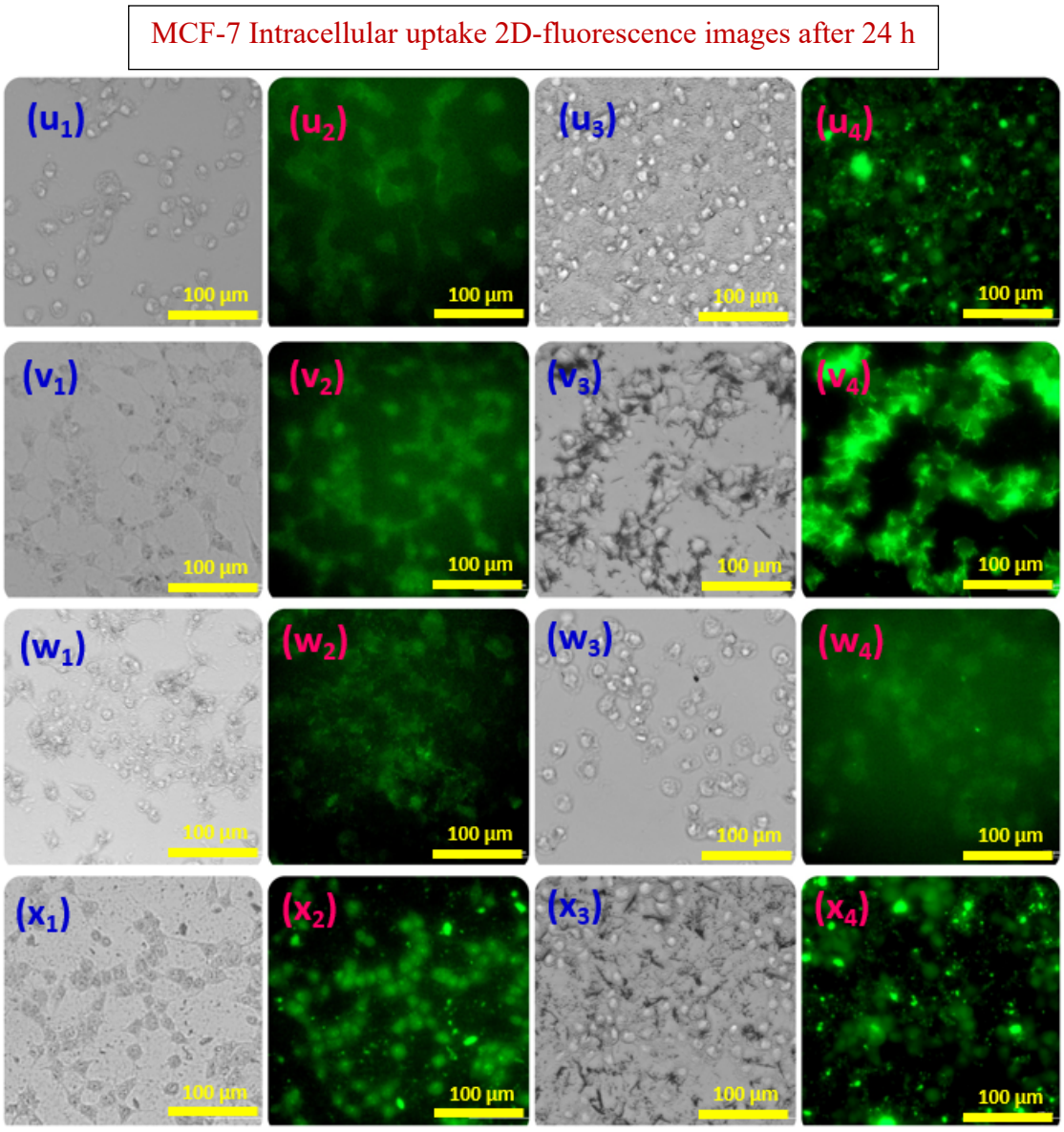


Figure S6. Intracellular uptake 2D-fluorescence images after zero moment, 4 h and 24 h of treatments at 37°C with 95% humidity. Excitation wavelength, 360 nm. Wavelength ranges, 500–570 nm for green channel.

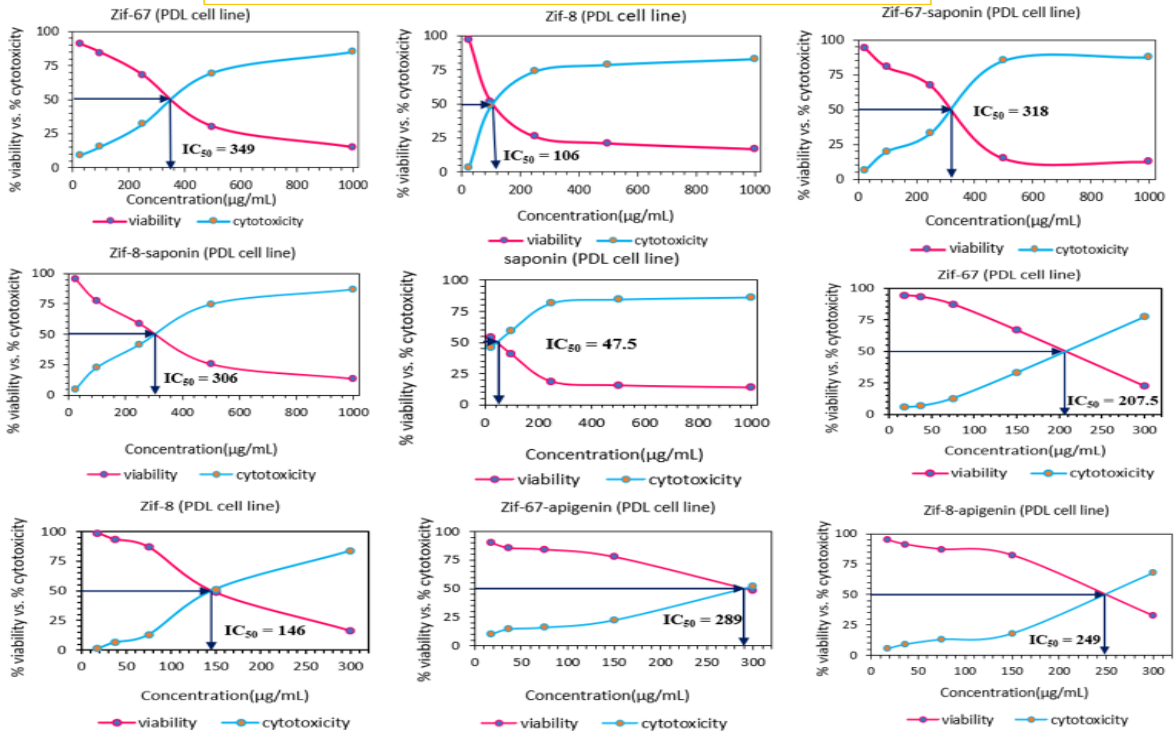
Intracellular uptake 2D-fluorescence images after zero moment (MCF-7 Cell) :(m_1,m_2)ZIF-67, (m_3,m_4) ZIF-8 , (n_1,n_2) Saponin , (n_3,n_4) Apigenin , (o_1,o_2) ZIF-67-Saponin, (o_3,o_4) ZIF-67-Apigenin , (p_1,p_2) ZIF-8-Saponin , (p_3,p_4) ZIF-8-Apigenin.

Intracellular uptake 2D-fluorescence images after 4 h (MCF-7 Cell) : (q_1,q_2)ZIF-67, (q_3,q_4) ZIF-8 , (r_1,r_2) Saponin , (r_3,r_4) Apigenin , (s_1,s_2) ZIF-67-Saponin, (s_3,s_4) ZIF-67-Apigenin , (t_1,t_2) ZIF-8-Saponin , (t_3,t_4) ZIF-8-Apigenin.

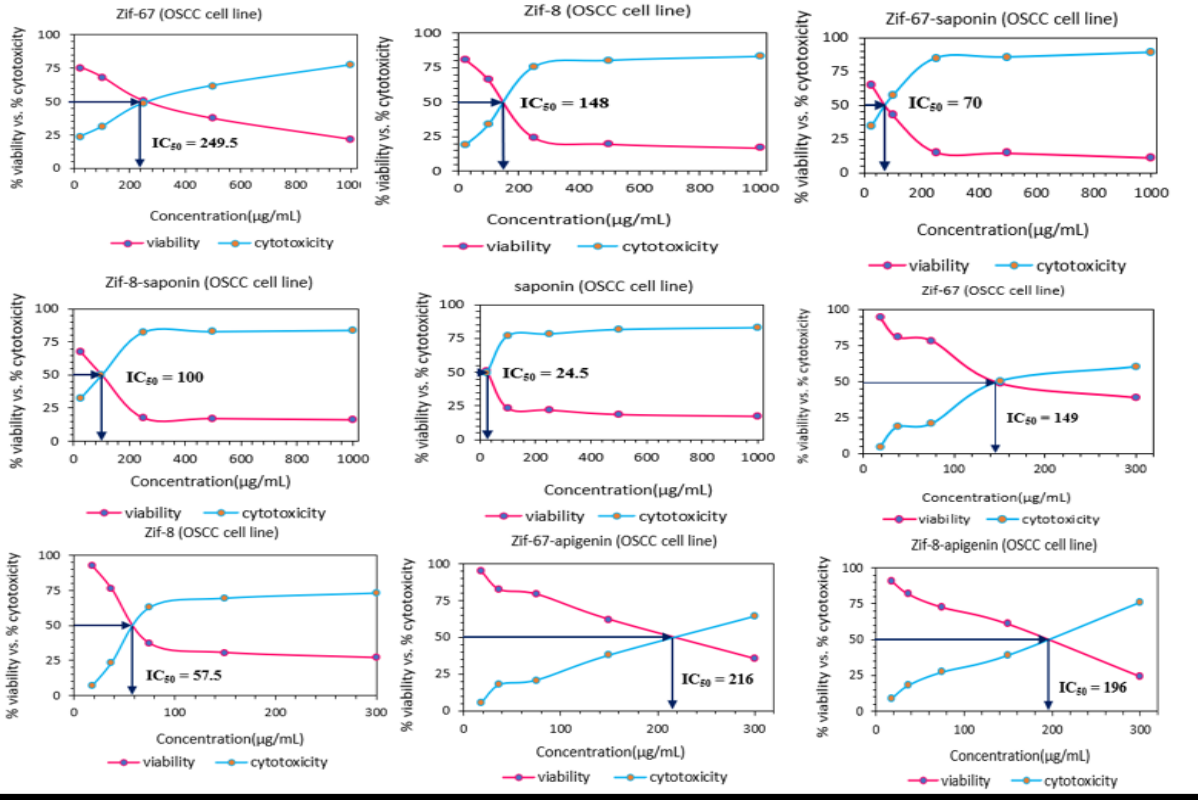
Intracellular uptake 2D-fluorescence images after 24 h (MCF-7 Cell) : (u_1,u_2)ZIF-67, (u_3,u_4) ZIF-8 , (v_1,v_2) Saponin , (v_3,v_4) Apigenin , (w_1,w_2) ZIF-67-Saponin, (w_3,w_4) ZIF-67-Apigenin , (x_1,x_2) ZIF-8-Saponin , (x_3,x_4) ZIF-8-Apigenin.

IC_{50} diagrams:

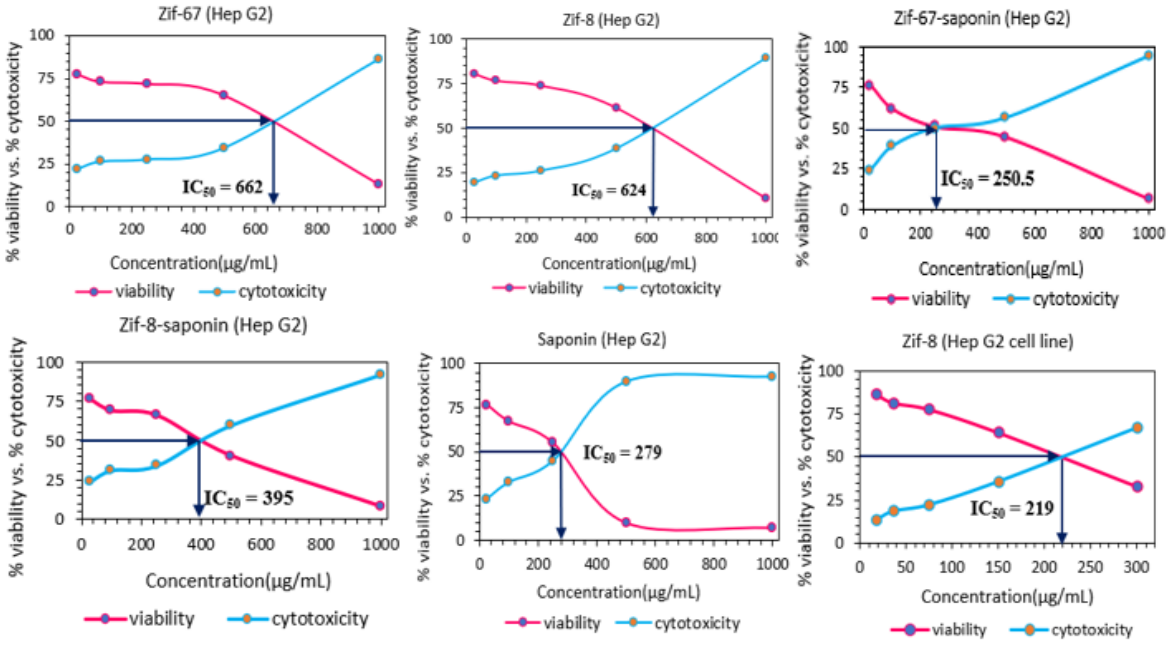
IC50 compounds on the PDL cell line



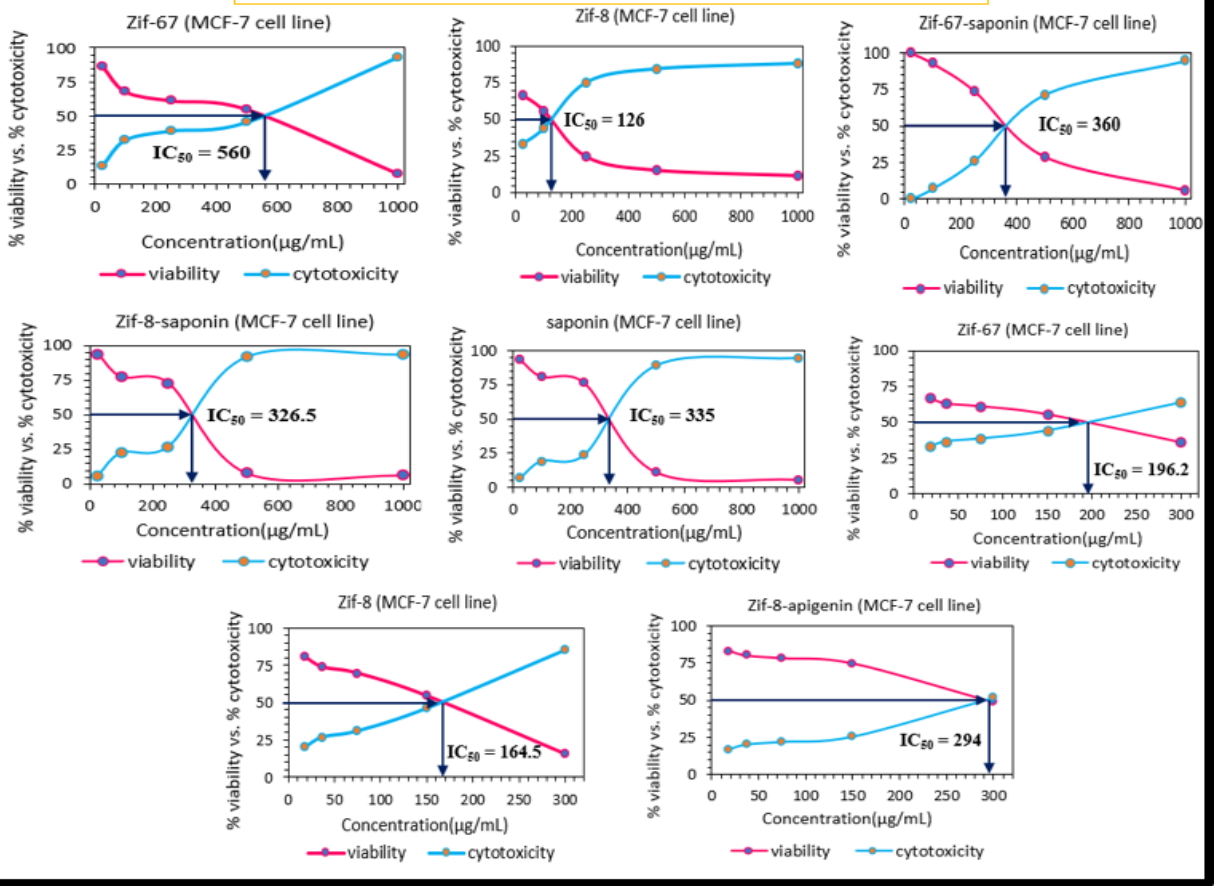
IC50 compounds on the OSCC cell line



IC50 compounds on the Hep-G2 cell line



IC50 compounds on the MCF-7 cell line



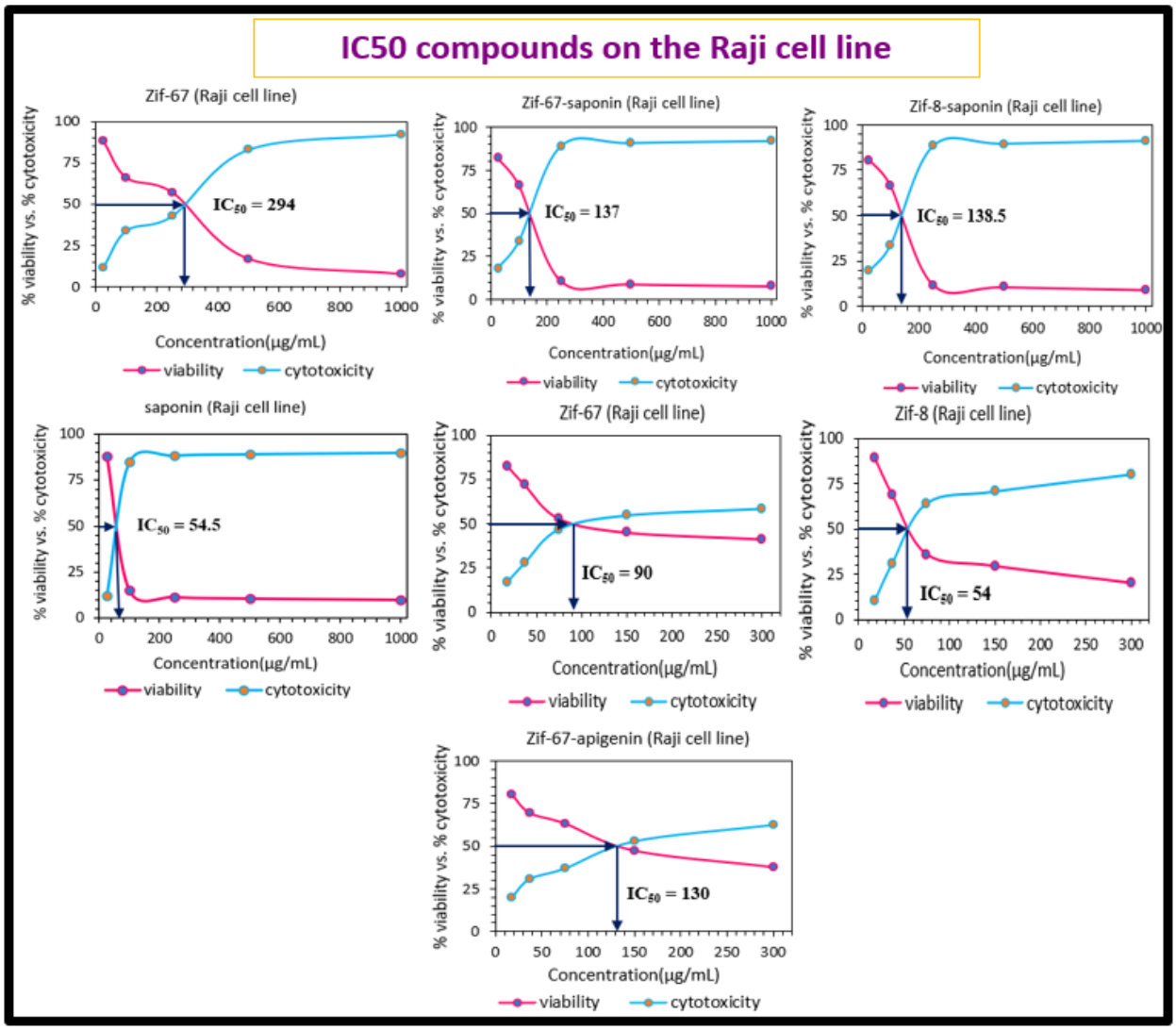


Figure S7. IC_{50} diagrams of samples treated with PDL, OSCC, Hep-G2, MCF-7 and Raji cell lines.